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Controlled Release Gastroretentive dosage form of Verapamil Hydrochloride

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Abstract: The objective of the present investigation was to develop a gastroretentive tablets for verapamil hydrochloride (verapamil-HCl) using different hydrocolloid polymers including Carbopol (CP 934P; CP 940P), Hydroxypropylmethylcellulose (HPMC K4M; HPMC K15 M; HPMC E15) and Xanthan gum by direct compression technology. The tablets were evaluated for the physicochemical parameters such as weight variation, thickness, friability, hardness, drug content, in vitro buoyancy studies, swelling index study, in vitro dissolution studies. The prepared tablets exhibited satisfactory physico-chemical characteristics. Tablet bouncy was achieved by adding an effervescent mixture of sodium bicarbonate and anhydrous citric acid. The *in vitro* dissolution studies were carried out in a USP XXII apparatus 2 in 0.1N HCl. All the gastroretentive tablets showed good in-vitro buoyancy. The tablet swelled radially and axially during in-vitro buoyancy studies. The selected tablets (F6) containing Xanthan gum released approximately 97.89% drug in 24 h in vitro dissolution study, while the buoyancy lag time was 24.6 ± 3.2 second and the tablet remained buoyant for > 24 h. Zero order and non-Fickian release transport was confirmed as the drug release mechanism for the selected tablets (F6). Tablets (F6) showed no significant change in physical appearance, drug content, total buoyancy time or *in vitro* dissolution study after storage at 45 °C/75% RH for three months.

Keywords: floating tablet, controlled release, verapamil hydrochloride, gastroretentive,

Introduction

A controlled drug delivery system with prolonged residence time in the stomach is of particular interest for drugs that (i) are locally active in the stomach, (ii) have an absorption window in the stomach or in the upper small intestine, (iii) are unstable in the intestinal or colonic environment, (iv) exhibit low solubility at high pH values[1]. The controlled gastric retention of solid dosage forms may be achieved by the mechanisms of flotation[2], mucoadhesion[3], sedimentation[4], expansion[5],modified shape systems[6],or by the simultaneous administration of pharmacological agents that delay gastric emptying. Gastro retentive drug delivery systems can improve the controlled delivery of drugs that have an absorption window in the stomach by continuously releasing the drug for a prolonged period of time, thus ensuring its optimal bioavailability[7].

Verapamil HCl is a calcium channel blocker used in the treatment of several cardiovascular disorders, particularly angina pectoris, supraventricular tachycardia and hypertension[8]. It is established that 90% of verapamil HCl is absorbed following its oral administration and then it reaches maximum plasma concentration within 1-2% hours. However, due to first pass effect it has low bioavailability (10-20%) [9]. It has short half- life of 4 hours, so dosing frequency is high. The physicochemical properties of verapamil HCl and its short half life make its suitable candidate for preparation of gastroretantive tablets.

The objective of present investigation is to prepare and evaluate gastroretentive tablets of verapamil HCl based on gel forming polymers using hydroxypropylmethyl cellulose (K4M, K15M and HPMC E15), carbopol (934P and 940P), xanthan gum BP which will help to retain the dosage form in the stomach. The selected tablets were used for stability studies for three months.

Materials and Methods

Verapamil HCl, Hydroxypropylmethylcellulose K4M (HPMC K4M), HPMC K15M, HPMC E15 and Xanthan gum BP were procured as gift samples from Torrent Laboratory Ltd., Ahmedabad, India. Polyvinylpyrolidon

(PVP K30), Carbopol 934P (CP 934P) and Carbopol 940P (CP 940P), Sodium bicarbonate, Anhydrous citric acid were procured from S.D. Fine Chemicals Ltd., Mumbai., India. All other materials were of analytical grade.

Preparation of gastro retentive tablets

The tablets of verapamil HCl (320 mg equivalent to 120 mg of verapamil HCl) were prepared by mixing required quantities of HPMC K4 M/ HPMC K15M/ CP 934P/CP 940P /Xanthan gum, Sodium bicarbonate, and Anhydrous citric acid by using PVP K30 in ethanol (96% v/v) as a granulating agent. Bouyancy of tablets was achieved by adding an effervescent mixture of sodium bicarbonate and anhydrous citric acid. The granules were dried at 60°C for 30 minutes in an oven and then lubricated with magnesium stearate and purified talc. The granules were compressed into tablets using a by a single punch tablet compression machine (Cadmach, Ahmedabad, India) fitted with 12 mm flat-faced punches. Compression was controlled to produce a 5 kg/cm^2 tablet crushing strength. The tablet composition of gastoretentive tablets are shown in Table 1.

Table 1: Composition of Gastroretentive tablets of verapamil HCL (F1 to F6)

Ingredients (mg/tablet)	F_1	F_2	F_3	F_4	F_5	F_6
Verapamil-HCL	120	120	120	120	120	120
CP 934 P	100	-	-	-	-	-
CP 940 P	-	100	-	-	-	-
HPMC K4 M	-	-	100	-	-	-
HPMC K15M	-	-	-	100	-	-
HPMC E15					100	
Xanthan gum BP	-	-	-	-	-	100
Sodium bicarbonate	50	50	50	50	50	50
Anhydrous citric acid	20	20	20	20	20	20
Talc	5	5	5	5	5	5
Magnesium stearate	5	5	5	5	5	5
PVP K30	20	20	20	20	20	20

In vitro buoyancy studies

The buoyancy studies were performed by placing the tablet in a 250 ml glass beaker, containing 200 ml of 0.1N HCl with tween-20 (0.02% w/v), pH 1.2, maintained at 37 ± 0.5°C in a water bath[10]. Their physical state was observed for 24 h. The time between introduction of the dosage form and its buoyancy on the 0.1N HCl (buoyancy lag time) and the time during which the dosage form remains buoyant (total buoyancy time) were determined visually. Three replicates of each formula were performed.

Swelling study

Gastro retentive tablet was weighed individually (designated as W1) and placed separately in glass beaker containing 200 ml of 0.1N HCl and incubated at 37ºC ± 1ºC. At regular 1h time intervals until 24h, the tablet was removed from beaker, and the excess surface liquid was removed carefully using the filter paper. The swollen tablet was then re-weighed (W2) and swelling index (SI) was calculated using the following formula[11].

$$SI = (W2 - W1)/W1 \quad (1)$$

In vitro dissolution studies

The dissolution studies were performed by using a USP XXII paddle apparatus (Disso 2000, Lab India, Mumbai, India) at a rotational speed of 50 rpm. Exactly 900 mL of 0.1N HCl was used as the dissolution medium and maintained at 37°C ± 1°C. Then, 5 mL of the dissolution medium was taken out at 30 minutes, 1 hour, and thereafter every hour for 24 hours. Exactly 5 mL of fresh medium was added to the dissolution vessel after each withdrawal, to maintain a constant volume. The samples withdrawn were analyzed by using a UV spectrophotometer (Elico model, Mumbai, India) at 278 nm.

Stability studies

To assess the drug and formulation stability, stability studies were done according to ICH and WHO guidelines[12]. The prepared gastroretentive tablets containing xanthan gum (F6) was selected for stability study on the basis of in vitro controlled drug release, in vitro buoyancy studies, buoyancy lag time (S), total buoyancy time (h) and their physical properties. The selected tablets of verapamil HCl (F6) packed in high density polyethylene bottle, and various replicates were kept in the humidity chamber maintained at 40 °C and 75% RH for 3 months[13] (Yorco Scientific Industries, India). At the end of studies, samples were analyzed for the drug content, in vitro dissolution, floating behavior and other physicochemical parameters.

Results and Discussion:

Gestroretentive tablets of verapamil-HCl were developed to increase the gastric residence time of the drug, so that they can be retained in stomach for longer time and help in controlled release of drug up to 24 h. The tablets were made using different gel forming polymers such as CP 934P, CP 940P, HPMC K4M, HPMC K15M, HPMC E15, and Xanthan gum BP to optimize the drug content, in vitro buoyancy, swelling index and in vitro drug dissolution studies. The selection of viscosity grade of a

Table 2: Physicochemical Characterizations of Gastroretentive tablets of verapamil HCL (F1 to F6)

Evaluation Parameters	F_1	F_2	F_3	F_4	F_5	F_6
Thickness (mm)	2.47 ± 0.035	2.54 ± 0.070	2.53 ± 0.084	2.37 ± 0.041	2.41 ± 0.053	2.61 ± 0.049
Average weight (mg)	409.8 ±0.213	409.3± 0.224	410.9± 0.168	411.4± 0.141	411.7± 0.186	414.4± 0.132
Weight variation (%)	0.750± 0.005	0.692± 0.004	0.689± 0.004	0.636± 0.004	0.393± 0.002	0.479± 0.003
Hardness (Kg/cm^2)	5 ± 0.265	5. ± 0.170	5. ± 0.196	5. ± 0.165	5. ± 0.172	5. ± 0.198
Friability (%)	0.718 ± 0.060	0.869 ± 0.084	0.683 ± 0.063	0.702 ± 0.035	0.621 ± 0.030	0.719 ± 0.058
Drug content (mg/tablet)	121.4 ± 0.702	119.1 ± 0.707	119.3 ± 0.495	120.9 ± 0.636	118.4 ± 0.424	119.8 ± 0.141
Buoyancy lag time (S)	32.3 ± 4.0	78.9 ± 2.5	47.8 ± 3.1	53.1 ± 1.9	107.8 ± 4.4	24.6 ± 3.2
Total buoyancy Time (h)	> 24 hrs	> 24 hrs	14.53 ± 0.207	22.23 ± 0.011	4.15 ± 0.169	> 24 hrs
Buoyancy on disturbing	Float	Settle	Float	Float	Settle	Float

Table 3: kinetic models for Gastroretentive tablets of verapamil HCL (F1 to F6)

Code	Zero order		First order		Higuchi		Korsemeyer - Peppas	
	R^2	K_0 (mg/h^{-1})	R^2	K_1 (h^{-1})	R^2	K ($mg.h^{-1/2}$)	R^2	*n*
F1	0.9918	2.6573	0.9449	0.0725	0.9793	16.308	0.9866	0.5726
F2	0.9969	2.7295	0.9688	0.0585	0.9743	16.243	0.9915	0.5611
F3	0.9972	4.5870	0.8007	0.1633	0.9713	22.749	0.9959	0.6770
F4	0.9839	2.0830	0.9437	0.0725	0.9794	12.837	0.9907	0.5377
F5	0.9904	2.3586	0.8569	0.1053	0.9758	18.267	0.9934	0.5529
F6	0.9981	2.6539	0.9599	0.0912	0.9657	16.201	0.9912	0.6076

polymer is an important consideration in the formulation of tablet[14].

Different grade of viscosity of CP 934P, CP 940P, HPMC K4M, HPMC K15M, HPMC E15 and Xanthan gum polymers is known to be beneficial in improving floating (buoyancy) property[10]and release characteristics. When a combination of gas entrapping as well as controlled release system is there, the use of disintegrating agent is important which does not quickly break the matrix and allows slow disintegration of the swollen matrix. PVP K30 in an optimized concentration (20mg/tablet) was employed for such unique disintegration properties[15]**.** Talc, and magnesium stearate were employed for their glidant and lubricant property. The prepared gastroretentive tablets were evaluated for thickness, weight variation, hardness, friability, drug content, swelling index, in vitro buoyancy studies, and in vitro drug dissolution studies. All the studies were performed in triplicate and results are expressed as mean ± S.D.

Table 4:Stability study of Gastroretentive tablets of verapamil HCL (F1)

Characteristic	1st month	2nd month	3th month
Physical appearance	Off white, smooth, flat faced	Off white, smooth, flat faced	Off white, smooth, flat faced
Weight variation (%)	0.501±0.003	0.489±0.003	0.472±0.003
Handiness (kg/cm^2)	5.5 ± 0.172	5.33 ± 0.235	5.00 ± 0.349
Friability (%)	0.738 ± 0.061	0.702 ± 0.060	0.751 ± 0.035
Swelling index (%) 12h	2.4± 0.643	2.2± 0.243	2.3± 0.440
Drug content (mg/tablet)	117.3 ± 0.643	117.5 ± 0.431	116.7 ± 0.781
Buoyancy lag time (s)	28 ± 4.1	29.3 ± 4.5	27.1 ± 4.9
Total buoyancy time (h)	25.03 ± 0.041	28.81 ± 0.024	20.09 ± 0.056
Buoyancy on disturbing	Float	Float	Float
***In vitro* release (%) 24 h.**	84.19	87.45	88.18

Physical characterization of floating tablets

The gastroretentive verapamil HCl tablets were off-white, smooth and flat in appearnce. The results of physical characterizations are shown in Table 2.The thickness of tablets was measured by digital thickness tester (Mitutoyo, Japan) and was ranged between 2.41 ± 0.053 to 2.61 ± 0.049 mm. The weight variation for different formulations (F1 to F6) was found to be 0.393± 0.002 to 0.750±0.005 %, indicating consistency in each batch. The hardness of the tablets was measured by Monsanto tester (Indian Equipment Corporation (IEC) Mumbai, India) and was in between 5. ±0.165 to 5 ± 0.265kg/ cm^2. The friability was measured by Friabilator (Thermonik, Campbell Electronics, Mumbai) and was found to be 0.621 ± 0.030 to 0.869 ± 0.084%, which is an indication of satisfactory mechanical resistance of the tablets. The drug content was found to be 118.4 ± 0.424 to 121.4 ± 0.702mg with low standard deviation indicating batch-to-batch consistency.

***In vitro* buoyancy studies**

All the formulations were prepared by effervescent approach. Sodium bicarbonate induced carbon dioxide in the presence of dissolution medium. The combination of sodium bicarbonate and anhydrous citric acid provided desired floating ability and therefore this combination was selected (5:2) for the formulation of the gastroretentive tablets so as not to compromise the matrix integrity with the possible shortest bouncy lag time and floating duration of up to 24 h. It was observed that the gas generated is trapped and protected within the gel formed by hydration of polymers, thus decreasing the density of the tablet below 1 (one) and tablet becomes buoyant[16].

The gastroretentive tablets (F3, F4, and F5) with HPMC K4, HPMC K15, HPMC E15 exhibited buoyancy lag time of 47.8 ± 3.1, 53.1 ±1.9, and 107.8 ± 4.4 seconds respectively and all floated for less duration of time (<24 h) as compared to tablets F1 , F2 and F6 which containing CP 934P, CP 940P,and xenthan gum respectively, with less buoyancy lag time of 32.3 ± 4.0, 42.9 ± 2.5 and 24.6 ± 3.2 seconds respectively, with total buoyancy time of more than 24 h (Table 2). The formulations F2 (CP 940P), and F5 (HPMC E15) settled on disturbing during dissolution studies which might be due to their higher moisture gain which was resulted in dramatic increase in swelling of tablets which in turn, showed decrease in floating capability upon disturbing. This indicated that molecular weight distribution or viscosity of gel forming polymers influenced the *in vitro* buoyancy.

Swelling study

Swelling is also a vital factor to ensure bouyancy and drug dissolutin of the formulation. Gastroretentive tablets composed of polymeric matrices build a gel layer around the tablet core when they come in contact with water. This gel layer governs the drug release from the formulation. The swelling index of gastroretentive tablets of F1 to F6 is shown in Fig.1. Tablets containing CP 934P and CP 940P (F1 and F2) showed less swelling index at the beginning but higher swelling index was observed at the end of 12 h. While HPMC K4, HPMC K15 and HPMC E15 (F3, F4 and F5) swelled rapidly at the beginning in 0.1 N HCl and could not remain their

matrix integrity upto 12 h. Tablets containing xenthan gum (F6) showed constant increasing in swelling index upto 12 h.

***In vitro* dissolution studies**

In vitro dissolution studies of all the formulations of gastroretentive tablets of verapamil HCl were carried out in 0.1N HCl. The study was performed for 24 h and cumulative drug release was calculated at every one hour time interval. The results are shown in Fig. 2. After 1 h the drug dissolved from gastroretentive tablets of CP F1 (16.57) and F2 (12.20) was less than tablets containing different grade of HPMC F3 (33.82), F4 (24.50) and F5 (41.41). This showed that HPMC hydrated more rapidly than CP in the presence of 0.1 N HCl. But the tablets containing CP showed the drug release up to 24 h in controlled manner without changing their physical integrity in dissolution medium. Moreover the HPMC containing tablets F3, F4 and F5 could not bear their matrix shape until 24 h and the released the drug before 24 h. Tablets F3 could not remain its matrix integrity more than 16 h with release of 96.40 % of drug. Tablets F4 Showed release of 99.17% at the end of 22 h; and F5 lost their integrity just after 5 h with release of 99.88 % of drug. Tablets containing Xenthan gum (F6) showed constant drug release up to 24 hr (93.33). This controlled release of drug from F6 could be attributed to the formation of a thick gel structure that delays drug release from the tablet matrix.

The data obtained from *in vitro* dissolution studies were fitted to zero-order, first-order, Higuchi and Korsemeyer-Peppas equations (Table 3). The zero-order plots were found to be fairly linear as indicated by their high regression values. To confirm the exact mechanism of drug release, the data were fitted according to Korsemeyer-Peppas equation[17].

$$m_t/m_\alpha = k\, t^n \qquad (2)$$

Where, m_t/m_α is fraction of drug released, k is kinetic constant, t is release time and n is the diffusional exponent for drug release. Peppas stated that the above equation could adequately describe the release of solutes from slabs, spheres, cylinders and discs, regardless of the release mechanism. 'n' is the slope value of log m_t/m_α versus log time curve. The value of 'n' gives an indication of the release mechanism; when n = 1, the release rate is independent of time (zero-order) (case II transport), n = 0.5 for Fickian diffusion and when 0.5 < n <1.0, diffusion and non-Fickian transport are implicated. Lastly, when n > 1.0 super case II transport is apparent. Slope values (0.5<n<1.0) suggest that the release of verapamil HCl from gastroretentive tablets followed non-Fickian diffusion mechanism.

Stability studies

The prepared gastroretentive tablets containing Xanthan gum (F6) was selected for stability study on the basis of in vitro buoyancy and in vitro drug dissolution studies. The tablets were investigated at 40 °C/75%RH in both opened and closed high density polyethylene bottles for 3 months. The drug release rate from the gastroretentive tablets of verapamil HCL showed no significant change during storage (Table 4). Thus, it was found that the gastroretentive tablets of verapamil HCL tablets (F6) were stable under these storage conditions for at least 3 months.

Figure1: Swelling index of Gastroretentive tablets of verapamil HCL (F1 to F6)

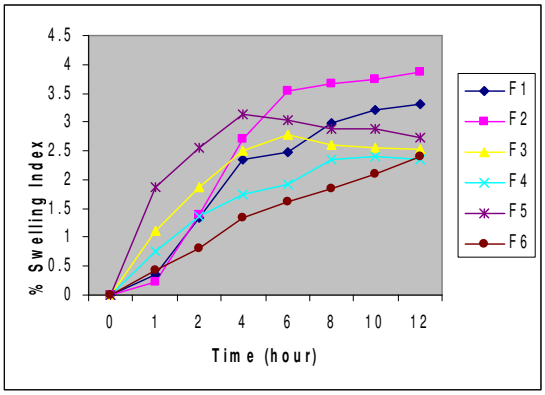
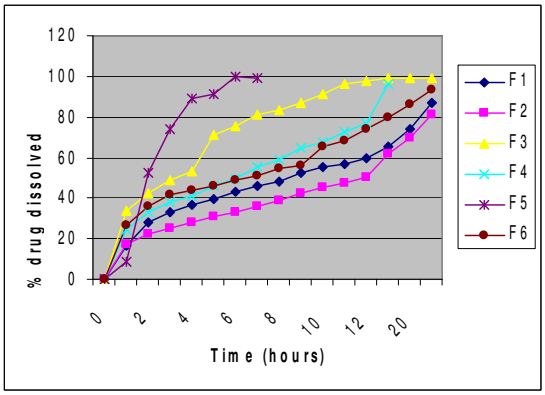
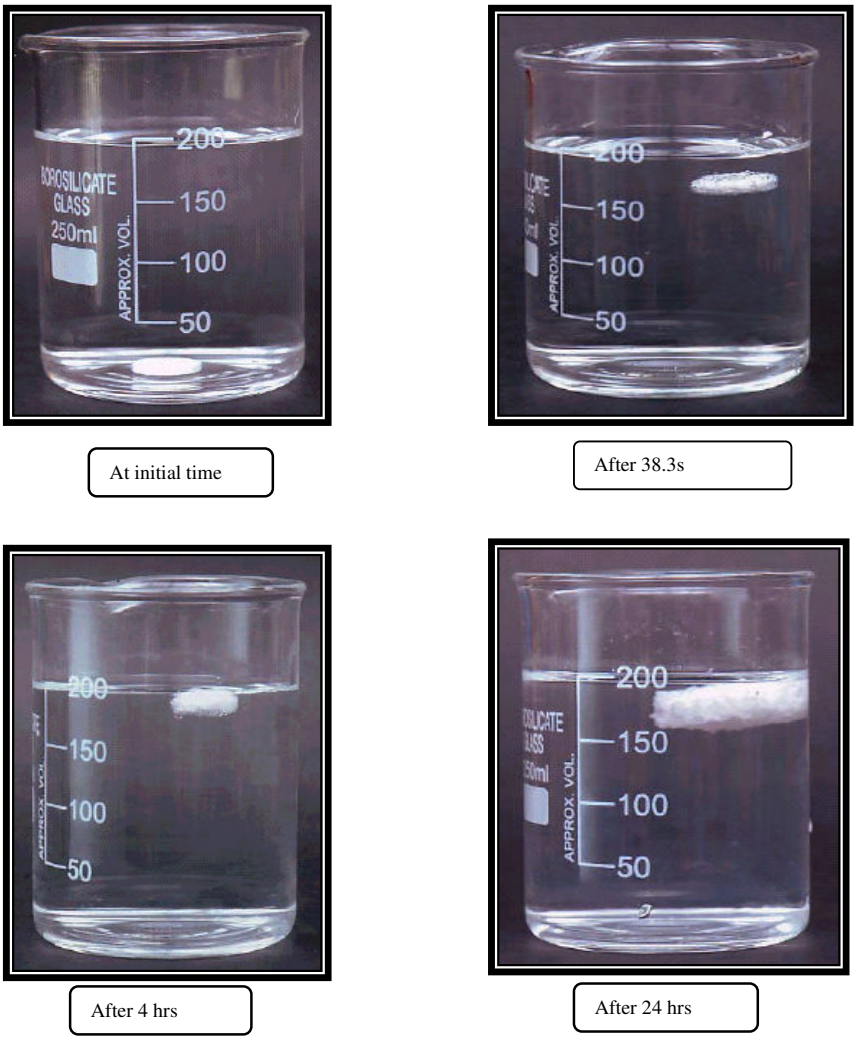


Figure 2: Cumulative percentage drug dissolved from gastroretentive tablets of Verapamil HCL (F1 to F6)



Conclusion

Gastroretentive tablets of verapamil hydrochloride were successfully formulated in effervescent technique. Tablets containing xanthan gum along with citric acid and sodium bicarbonate showed short buoyancy lag time 24.6 second, total floating time more than 24h, which was a controlled release characteristic for 24 h. Good stability was observed for 3 months during stability studies.



Figur: 3 *In vitro* buoyancy studies (F6)

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